Terrestrial Animal Health Standards Report
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APPENDIX 3.9.3.

GUIDELINES FOR THE RESPONSIBLE AND PRUDENT USE OF ANTIMICROBIAL AGENTS IN VETERINARY MEDICINE

Article 3.9.3.1.

Purpose

These guidelines provide guidance for the responsible and prudent use of antimicrobials in veterinary medicine, with the aim of protecting both animal and human health. The competent authorities responsible for the registration and control of all groups involved in the production, distribution and use of veterinary antimicrobials have specific obligations.

Prudent use is principally determined by the outcome of the marketing authorisation procedure and by the implementation of specifications when antimicrobials are administered to animals.

Article 3.9.3.2.

Objectives of prudent use

Prudent use includes a set of practical measures and recommendations intended to prevent and/or reduce the selection of antimicrobial-resistant bacteria in animals to:

1) maintain the efficacy of antimicrobial agents and to ensure the rational use of antimicrobials in animals with the purpose of optimising both their efficacy and safety in animals;

2) comply with the ethical obligation and economic need to keep animals in good health;

3) prevent, or reduce, as far as possible, the transfer of bacteria (with their resistance determinants) within animal populations;

4) maintain the efficacy of antimicrobial agents used in food-producing animals ~~livestock~~;

5) prevent or reduce the transfer of resistant bacteria or resistance determinants from animals to humans;

6) maintain the efficacy of antimicrobial agents used in human medicine and prolong the usefulness of the antimicrobials;

7) prevent the contamination of animal-derived food with antimicrobial residues that exceed the established maximum residue limit (MRL);

8) protect consumer health by ensuring the safety of food of animal origin.

Article 3.9.3.3.

Responsibilities of the regulatory authorities

1) Marketing authorisation

The national regulatory authorities are responsible for granting marketing authorisation. This should be done in accordance with the provisions of the *Terrestrial Code*. They have a significant role in specifying the terms of this authorisation and in providing the appropriate information to the veterinarian.

2) Submission of data for the granting of the marketing authorisation

The pharmaceutical industry has to submit the data requested for the granting of the marketing authorisation. The marketing authorisation is granted only if the criteria of safety, quality and efficacy are met. An assessment of the potential risks and benefits to both ~~the~~ animals and humans ~~the consumer~~ resulting from the use of antimicrobial agents in food-producing animals should ~~must~~ be carried out. The evaluation should focus on each individual antimicrobial product and the findings not be generalised to the class of antimicrobials to which the particular active principle belongs. ~~If dose ranges or different durations of treatment are suggested~~, Guidance on usage should be provided for all dose ranges or different durations of treatment that are proposed.

3) Market approval

Regulatory authorities should attempt to expedite the market approval process of a new antimicrobial in order to address a specific need for the treatment of disease.

4) Registration procedures

Countries lacking the necessary resources to implement an efficient registration procedure for veterinary medicinal products (VMPs), and whose supply principally depends on imports from foreign countries, should ~~must~~ undertake the following measures:

a) check the efficacy of administrative controls on the import of these VMPs;

b) check the validity of the registration procedures of the exporting and manufacturing country as appropriate;

c) develop the necessary technical co-operation with experienced authorities to check the quality of imported VMPs as well as the validity of the recommended conditions of use.

Regulatory authorities of importing countries should request the pharmaceutical industry to provide quality certificates prepared by the competent authority of the exporting and manufacturing country as appropriate. All countries should make every effort to actively combat the manufacture, advertisement, trade, distribution and use of unlicensed and counterfeit bulk active pharmaceutical ingredients and products.

5) Quality control of antimicrobial agents

Quality controls should be performed:

a) in compliance with the provisions of good manufacturing practices;

b) to ensure that analysis specifications of antimicrobial agents used as active ingredients comply with the provisions of approved monographs;

c) to ensure that the quality and concentration (stability) of antimicrobial agents in the marketed dosage form(s) are maintained until the expiry date, established under the recommended storage conditions;

d) to ensure the stability of antimicrobials when mixed with feed or drinking water;

e) to ensure that all antimicrobials are manufactured to the appropriate quality and purity in order to guarantee their safety and efficacy.

6) Assessment ~~Control~~ of therapeutic efficacy

a) Preclinical trials

i) Preclinical trials should:

– establish the range of activity of antimicrobial agents on both pathogens and non-pathogens (commensals);

– assess the ability of the antimicrobial agent to select for resistance ~~resistant bacteria~~ *in vitro* and *in vivo,* taking into consideration pre-existing resistant strains;

– establish an appropriate dosage regimen necessary to ensure the therapeutic efficacy of the antimicrobial agent and limit the selection of antimicrobial resistance ~~resistant bacteria~~. (Pharmacokinetic pharmacodynamic data and models can assist in this appraisal.)

ii) The activity of antimicrobial agents towards the targeted micro-organism ~~bacteria~~ should be established by pharmacodynamics. The following criteria should be taken into account:

– mode and spectrum of activity ~~action~~;

– minimum inhibitory and bactericidal concentrations;

– time- or concentration-dependent activity or co-dependency;

– activity at the site of infection.

iii) The dosage regimens allowing maintenance of effective antimicrobial levels should be established by pharmacokinetics. The following criteria should be taken into account:

– bio-availability according to the route of administration;

– concentration of the antimicrobial at the site of infection and its distribution in the treated animal;

– metabolism that may lead to the inactivation of antimicrobials;

– excretion routes;

– use of combinations of antimicrobial agents should be scientifically supported ~~justified~~.

b) Clinical trials

Clinical trials should be performed to confirm the validity of the claimed therapeutic indications and dosage regimens established during the preclinical phase. The following criteria should be taken into account:

i) diversity of the clinical cases encountered when performing multi-centre trials;

ii) compliance of protocols with good clinical practice, such as Veterinary International Cooperation on Harmonisation (VICH) guidelines;

iii) eligibility of studied clinical cases, based on appropriate criteria of clinical and bacteriological diagnoses;

iv) parameters for qualitatively and quantitatively assessing the efficacy of the treatment.

7) Assessment of the potential of antimicrobials to select for resistance ~~resistant bacteria~~

Other studies may be requested in support of the assessment of the potential of antimicrobials to select for resistance ~~resistant bacteria~~. ~~The interpretation of their results should be undertaken with great caution~~. The party applying for market authorisation should, where possible, supply data derived in target animal species under the intended conditions of use.

For this the following may be considered ~~Considerations may include~~:

a) the concentration of active compound in the gut of the animal (where the majority of potential food-borne pathogens reside) at the defined dosage level;

b) the route and level of human exposure to food-borne or other resistant organisms ~~bacteria~~;

c) the degree of cross-resistance within the class of antimicrobials and between classes of antimicrobials;

d) the pre-existing level of resistance in the pathogens of human health concern (baseline determination) in both animals and humans.

~~Other studies may be requested in support of the assessment of the potential of antimicrobials to select for resistant bacteria. The interpretation of their results should be undertaken with great caution.~~

8) Establishment of acceptable daily intake, maximum residue level and withdrawal periods for antimicrobial compounds

a) When setting the acceptable daily intake (ADI) and MRL for an antimicrobial substance, the safety evaluation should also include the potential biological effects on the intestinal flora of humans.

b) The establishment of an ADI for each antimicrobial agent, and an MRL for each animal-derived food, should be undertaken.

c) For each VMP containing antimicrobial agents, withdrawal periods should be established in order to produce food in compliance with the MRL, taking into account:

i) the MRL established for the antimicrobial agent under consideration;

ii) the composition of the product and the pharmaceutical form;

iii) the target animal species;

iv) the dosage regimen and the duration of treatment;

v) the route of administration.

d) The applicant should provide methods for regulatory testing of residues in food.

9) Protection of the environment

An assessment of the impact of the proposed antimicrobial use on the environment should be conducted. Efforts should be made to ensure that the environmental impact of antimicrobial use ~~contamination with antimicrobials~~ is restricted to a minimum.

10) Establishment of a summary of product characteristics for each veterinary antimicrobial ~~medicinal~~ product (VAP)

The summary of product characteristics contains the information necessary for the appropriate use of VAPs ~~VMPs~~ and constitutes the official reference for their labelling and package insert. This summary should ~~always~~ contain the following items:

a) active ingredient and class,

b) pharmacological properties

c) any potential adverse effects,

d) target animal species,

e) therapeutic indications,

f) target micro-organisms ~~bacteria~~,

g) dosage and administration route,

h) withdrawal periods,

i) incompatibilities,

j) shelf-life ~~expiry date~~,

k) operator safety,

l) particular precautions before use,

m) particular precautions for the proper disposal of un-used or expired products,

n) information on conditions of use relevant to the potential for selection of resistance.

~~Antimicrobials that are considered to be important in treating critical diseases in humans should only be used in animals when alternatives are either unavailable or inappropriate.~~

~~Consideration should be given to providing such guidance by means of the product label and data sheet.~~

~~The oral route should be used with caution.~~

11) Post-marketing antimicrobial surveillance

The information collected through existing pharmacovigilance programmes, including lack of efficacy, should form part of the comprehensive strategy to minimise antimicrobial resistance. In addition to this the following should be considered:

a) General epidemiological surveillance

The surveillance of animal bacteria resistant to antimicrobial agents is essential. The relevant authorities should implement a programme according to the *Terrestrial Code*.

b) Specific surveillance

Specific surveillance to assess the impact of the use of a specific antimicrobial may be implemented after the granting of the marketing authorisation The surveillance programme should evaluate not only resistance development in target animal pathogens, but also in food-borne pathogens and/or commensals. Such surveillance will also contribute to general epidemiological surveillance of antimicrobial resistance.

12) Supply and administration ~~Distribution~~ of the antimicrobial agents used in veterinary medicine

The relevant authorities should ensure that all the antimicrobial agents used in animals are:

a) prescribed by a veterinarian or other ~~suitably trained and~~ *authorised* person;

~~b) delivered by an authorised animal health professional;~~

b) supplied only through licensed/authorised distribution systems;

c) administered to animals by a veterinarian or under the supervision of a veterinarian or by other authorised persons;

d) the relevant authorities should develop effective procedures for the safe collection and destruction of unused or expired VAPs.

13) Control of advertising

All advertising of antimicrobials should be controlled by a code of advertising standards, and the relevant authorities must ensure that the advertising of antimicrobial products:

a) complies with the marketing authorisation granted, in particular regarding the content of the summary of product characteristics;

b) is restricted to authorised professionals, according to national legislation in each country.

14) Training of antibiotic users

The training of users of antimicrobials ~~antibiotic users~~ should involve all the relevant organisations, such as regulatory authorities, pharmaceutical industry, veterinary schools, research institutes, veterinary professional organisations and other approved users such as food-animal owners. This training should focus on:

a) information on disease prevention and management strategies;

b) the ability of antimicrobials to select for resistance in food-producing animals;

c) the need to observe responsible use recommendations for the use of antimicrobial agents in animal husbandry in agreement with the provisions of the marketing authorisations.

15) Research

The relevant authorities should encourage public- and industry-funded research.

Article 3.9.3.4.

Responsibilities of the veterinary pharmaceutical industry

1) Marketing authorisation of VAPs ~~VMPs~~

The veterinary pharmaceutical industry has responsibilities to:

a) supply all the information requested by the national regulatory authorities;

b) guarantee the quality of this information in compliance with the provisions of good manufacturing, laboratory and clinical practices;

c) implement a pharmacovigilance programme and on request, specific surveillance for bacterial susceptibility and resistance.

2) Marketing and export of VAPs ~~VMPs~~

For the marketing and export of VAPs ~~VMPs~~:

a) only licensed and officially approved VAPs ~~VMPs~~ should be sold and supplied, and then only through licensed/authorised distribution systems;

b) the pharmaceutical industry should provide quality certificates prepared by the Competent Authority of the exporting and/or manufacturing countries to the importing country ~~only VMPs that have been authorised in the (exporting) country in which the product(s) is approved for sale or the quality of which is certified by a regulatory authority should be exported~~;

c) the national regulatory authority should be provided with the information necessary to evaluate the amount of antimicrobial agents marketed.

3) Advertising

The veterinary pharmaceutical industry should:

a) disseminate information in compliance with the provisions of the granted authorisation;

b) ensure that the advertising of antimicrobials directly to the food animal ~~livestock~~ producer is discouraged.

4) Training

The veterinary pharmaceutical industry should participate in training programmes as defined in point 14 of Article 3.9.3.3.

5) Research

The veterinary pharmaceutical industry should contribute to research as defined in point 15 of Article 3.9.3.3.

Article 3.9.3.5.

Responsibilities of wholesale and retail distributors ~~pharmacists~~

1) Retailers distributing VAPs ~~Pharmacists~~ should only do so on the prescription of a veterinarian or other suitably trained person authorised in accordance with national legislation and all products should be appropriately labelled ~~distribute veterinary antimicrobials on prescription. All products should be appropriately labelled (see point 5 of Article 3.9.3.6.)~~.

2) The guidelines on the responsible use of antimicrobials should be reinforced by retail distributors ~~pharmacists~~ who should keep detailed records of:

   a) date of supply,

   b) name of prescriber,

   c) name of user,

   d) name of product,

   e) batch number,

   f) quantity supplied.

3) Distributors ~~Pharmacists~~ should also be involved in training programmes on the responsible use of antimicrobials, as defined in point 14 of Article 3.9.3.3.

Article 3.9.3.6.

Responsibilities of veterinarians

The ~~prime~~ concern of the veterinarian is to promote public health and animal health and welfare. The veterinarian's responsibilities include preventing, identifying and treating animal diseases. The promotion of sound animal husbandry methods, hygiene procedures and vaccination strategies (good farming practice) can help ~~encourage good farming practice in order~~ to minimise the need for antimicrobial use in food-producing animals ~~livestock~~.

Veterinarians should only prescribe antimicrobials for animals under their care.

1) Use of antimicrobial agents

   The responsibilities of veterinarians ~~in this area~~ are to carry out a proper clinical examination of the animal(s) and then:

   a) only prescribe antimicrobials when necessary;

   b) make an appropriate choice of the antimicrobial based on experience of the efficacy of treatment.

   ~~On certain occasions, a group of animals that may have been exposed to pathogenic bacteria may need to be treated without recourse to an accurate diagnosis and antimicrobial susceptibility testing to prevent the development of clinical disease and for reasons of animal welfare.~~

2) Choosing an antimicrobial agent

a) The expected efficacy of the treatment is based on:

i) the clinical experience of the veterinarian;

ii) the activity towards the pathogens ~~pathogenic bacteria~~ involved;

iii) the appropriate route of administration;

iv) known pharmacokinetics/tissue distribution to ensure that the selected therapeutic agent is active at the site of infection;

v) the epidemiological history of the rearing unit, particularly in relation to the antimicrobial resistance profiles of the pathogens ~~pathogenic bacteria~~ involved.

Should a first-line antibiotic treatment fail or should the disease recur, a second line treatment should ideally be based on the results of diagnostic tests.

To minimise the likelihood of antimicrobial resistance developing, it is recommended that antimicrobials be targeted to pathogens ~~bacteria~~ likely to be the cause of infection.

On certain occasions, a group of animals that may have been exposed to pathogens may need to be treated without recourse to an accurate diagnosis and antimicrobial susceptibility testing to prevent the development of clinical disease and for reasons of animal welfare.

b) Use of combinations of antimicrobial agents should be scientifically supported. Combinations of antimicrobials may be ~~are~~ used for their synergistic effect to increase therapeutic efficacy or to broaden the spectrum of activity. ~~Furthermore, the use of combinations of antimicrobials can be protective against the selection of resistance in cases in which bacteria exhibit a high mutation rate against a given antimicrobial.~~

~~Some combinations of antimicrobials may, in certain cases, lead to an increase in the selection of resistance.~~

3) Appropriate use of the antimicrobial agent chosen

A prescription for antimicrobial agents should ~~must~~ indicate precisely the treatment regime, the dose, the treatment ~~dosage~~ intervals, the duration of the treatment, the withdrawal period and the amount of drug to be delivered, depending on the dosage and the number of animals to be treated.

The off-label use of a veterinary antimicrobial drug may be permitted in appropriate circumstances and should be in agreement with the national legislation in force including the withdrawal periods to be used. It is the veterinarian's responsibility to define the conditions of responsible use in such a case including the therapeutic regimen, the route of administration, and the duration of the treatment. ~~As far as 'Off label use' (extra label use) of veterinary medicinal products is concerned, although all medicinal products should be prescribed and used in accordance with the specifications of the marketing authorisation, the prescriber should have the discretion to adapt these in exceptional circumstances~~.

4) Recording

Records on veterinary antimicrobial drugs should be kept in conformity with national legislation. Information records should include the following ~~All available information should be consolidated into one form or database. This information should~~:

a) ~~allow monitoring of the~~ quantities of medication used;

b) ~~contain~~ a list of all medicines supplied to each food-producing animal ~~livestock~~ holding;

c) ~~contain~~ a list of medicine withdrawal periods ~~and a system for allowing information to be updated;~~

d) ~~contain~~ a record of antimicrobial susceptibilities;

e) ~~provide~~ comments concerning the response of animals to medication;

f) ~~allow~~ the investigation of adverse reactions to antimicrobial treatment, including lack of response due to antimicrobial resistance. Suspected adverse reactions should be reported to the appropriate regulatory authorities.

Veterinarians should also periodically review farm records on the use of VAPs to ensure compliance with their directions and use these records to evaluate the efficacy of treatment regimens.

5) Labelling

All medicines supplied by a veterinarian should be ~~adequately~~ labelled according to national legislation ~~with the following minimum information:~~

~~a) the name of the owner/keeper or person who has control of the animal(s);~~

~~b) the address of the premises where the animal(s) is kept;~~

~~c) the name and address of the prescribing veterinarian;~~

~~d) identification of the animal or group of animals to which the antimicrobial agent was administered;~~

~~e) the date of supply;~~

~~f) the indication 'For animal treatment only';~~

~~g) the warning 'Keep out of the reach of children';~~

~~h) the relevant withdrawal period, even if this is nil.~~

~~The label should not obscure the expiry date of the preparation, batch number or other important information supplied by the manufacturer~~.

6) Training

Veterinary professional organisations should participate in the training programmes as defined in point 14 of Article 3.9.3.3. It is recommended that veterinary professional organisations develop for their members species-specific clinical practice guidelines on the responsible use of VAPs.

Article 3.9.3.7.

Responsibilities of food-animal ~~livestock~~ producers

1) Food-animal ~~Livestock~~ producers with the assistance of a veterinarian, ~~where possible,~~ are responsible for ~~preventing outbreaks of disease and~~ implementing health and welfare programmes on their farms (good farming practice) in order to promote animal health.

2) Food-animal ~~Livestock~~ producers should ~~have to~~:

a) draw up a health plan with the attending veterinarian ~~in charge~~ that outlines preventative measures (feedlot health plans, mastitis control plans, endo- and ectoparasite control ~~worming~~ and vaccination programmes, etc.);

b) use antimicrobial agents only on prescription, and according to the provisions of the prescription;

c) use antimicrobial agents in the species, for the uses and at the dosages ~~doses~~ on the approved/registered labels and in accordance with product label instructions or the advice of a veterinarian familiar with the animals and the production site;

d) isolate sick animals, when appropriate, to avoid the transfer of pathogens ~~resistant bacteria~~. Dispose of dead or dying animals promptly under conditions approved by the relevant authorities;

e) comply with the storage conditions of antimicrobials in the rearing unit, according to the provisions of the leaflet and package insert;

f) address hygienic conditions regarding contacts between people (veterinarians, breeders, owners, children) and the animals treated;

g) comply with the recommended withdrawal periods to ensure that residue levels in animal-derived food do not present a risk for the consumer;

h) dispose of surplus antimicrobials under safe conditions for the environment; ~~partially used~~ medicines should only be used within the expiry date, for the condition for which they were prescribed and, if possible, in consultation with the prescribing veterinarian;

i) maintain all the laboratory records of bacteriological and susceptibility tests; these data should be made available to the veterinarian responsible for treating the animals;

j) keep adequate records of all medicines used, including the following:

i) name of the product/active substance and batch number,

ii) name of prescriber and/or the supplier,

iii) date of administration,

iv) identification of the animal or group of animals to which the antimicrobial agent was administered,

v) ~~diagnosis/~~clinical conditions treated,

vi) dosage ~~quantity of the antimicrobial agent~~ administered,

vii) withdrawal periods,

viii) result of laboratory tests,

ix) effectiveness of therapy;

k) inform the responsible veterinarian of recurrent disease problems.

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APPENDIX 3.9.4.

RISK ~~ANALYSIS~~ ASSESSMENT FOR ANTIMICROBIAL RESISTANCE ARISING FROM THE USE OF ANTIMICROBIALS IN ANIMALS

Article 3.9.4.1.

Guidelines for analysing the risks to animal and public health from antimicrobial resistant bacteria of animal origin

1) Introduction

The use of antimicrobials for therapy, prophylaxis and growth promotion in animals can reduce their efficacy in animal and human medicine, through the development of antimicrobial resistant strains of pathogenic bacteria. This risk may be represented by the loss of therapeutic efficacy of one or several antimicrobial drugs and includes the emergence of multi-resistant bacteria.

2) Objective

The principal aim of risk analysis for antimicrobial resistance in bacteria from animals is to provide Member Countries with a transparent, objective and scientifically defensible method of assessing and managing the human and animal health risks associated with the development of resistance arising from the use of antimicrobials in animals.

3) The risk analysis process

The principles of risk analysis are described in Section 1.3. of the *Terrestrial Code*.

A qualitative risk assessment should always be undertaken. Its outcome will determine whether progression to a quantitative risk assessment is feasible and/or necessary.

4) Hazard identification

For the purposes of this Appendix, the hazard is the resistance determinant that emerges as a result of the use of a specific antimicrobial in animals. This definition reflects the development of resistance in a species of pathogenic bacteria, as well as the development of a resistance determinant that may be passed from one species of bacteria to another. The conditions under which the hazard might produce adverse consequences include any ~~feasible~~ scenarios through which humans or animals could become exposed to a pathogen which contains that resistance determinant, fall ill and then be treated with an antimicrobial that is no longer effective because of the resistance.

5) Risk assessment

The assessment of the risk to human and animal health from antimicrobial-resistant bacteria resulting from the use of antimicrobials in animals should examine:

a) the likelihood of emergence of resistant bacteria arising from the use of antimicrobial(s), or more particularly, production of the resistant determinants if transmission is possible between bacteria;

b) consideration of all pathways and their importance, by which humans could be exposed to these resistant bacteria or resistance determinants, together with the possible ~~dose of bacteria in the~~ degree of exposure;

c) the consequences of exposure and the estimated probability of its occurrence.

Article 3.9.4.2.

Analysis of risks to human health

1) Definition of the risk

The infection of humans with bacteria that have acquired resistance to a specific antimicrobial used in animals, and resulting in the loss of benefit of antimicrobial therapy used to manage the human infection.

2) Hazard identification

- Bacteria that have acquired resistance, (including multiple resistance) arising from the use of an antimicrobial(s) in animals.

- Bacteria having obtained a resistance determinant(s) from other bacteria which have acquired resistance arising from the use of an antimicrobial(s) in animals.

The identification of the hazard must include consideration of the class or subclass of the antimicrobial(s). This definition should be read in conjunction with point 4) of Article 3.9.4.1.

3) Release assessment

A release assessment describes the biological pathways necessary for the use of a specific antimicrobial in animals to lead to the release of resistant bacteria or resistance determinants into a particular environment, and estimating either qualitatively or quantitatively the probability of that complete process occurring. The release assessment describes the probability of the release of each of the potential hazards under each specified set of conditions with respect to amounts and timing, and how these might change as a result of various actions, events or measures.

The following factors should be considered in the release assessment:

- species of animal treated with the antimicrobial(s) in question
- number of animals treated, geographical distribution of those animals
- amounts used and duration of treatment
- variation in methods and routes of administration of the antimicrobial(s)
- the pharmacodynamics/pharmacokinetics of the antimicrobial(s)
- bacteria developing resistance as a result of the antimicrobial(s) use
- mechanism of direct or indirect transfer of resistance
- cross-resistance and/or co-resistance with other antimicrobials
- surveillance of animals, ~~animal~~ products of animal origin and animal waste products for the existence of resistant bacteria.

Appendix XXI (contd)

4) Exposure assessment

An exposure assessment describes the biological pathways necessary for exposure of humans to the resistant bacteria or resistance determinants released from a given antimicrobial use in animals, and estimating the probability of the exposures occurring. The probability of exposure to the identified hazards is estimated for specified exposure conditions with respect to amounts, timing, frequency, duration of exposure, routes of exposure and the number, species and other characteristics of the human populations exposed.

The following factors should be considered in the exposure assessment:

- human demographics and food consumption patterns, including traditions and cultural practices
- prevalence of resistant bacteria in food
- ~~animal environment contaminated~~ environmental contamination with resistant bacteria
- prevalence of animal feed contaminated with resistant bacteria
- cycling of resistant bacteria between humans, animals and the environment
- steps of microbial decontamination of food
- microbial load in contaminated food at the point of consumption
- survival capacity and redistribution of resistant bacteria during the food production process (including slaughtering, processing, storage, transportation and retailing)
- disposal practices for waste products and the opportunity for human exposure to resistant bacteria or resistance determinants in those waste products
- point of consumption of food (professional catering, home cooking)
- variation in consumption and food-handling methods of exposed populations and subgroups of the population
- capacity of resistant bacteria to become established in ~~human intestinal flora~~ humans
- human-to-human transmission of the bacteria under consideration
- capacity of resistant bacteria to transfer resistance to human commensal bacteria and zoonotic agents
- amount and type of antimicrobials used in response to human illness
- dose, route of administration (oral, parenteral) and duration of human treatment
- pharmacokinetics (metabolism, bioavailability, access to intestinal flora).

5) Consequence assessment

A consequence assessment describes the relationship between specified exposures to resistant bacteria or resistance determinants and the consequences of those exposures. A causal process must exist by which exposures produce adverse health or environmental consequences, which may in turn lead to socio-economic consequences. The consequence assessment describes the potential consequences of a given exposure and estimates the probability of them occurring.

The following factors should be considered in the consequence assessment:

- dose–response relationships
- variation in disease susceptibility of exposed populations or subgroups of those populations
- variation and frequency of human health effects resulting from loss of efficacy of antimicrobials
- changes in human medicinal practices resulting from reduced confidence in antimicrobials
- changes in food consumption patterns due to loss of confidence in the safety of food products and any associated secondary risks
- associated costs
- interference with ~~a classical~~ first line/choice antimicrobial therapy in humans
- perceived future usefulness of the antimicrobial (time reference)
- prevalence of resistance in human bacterial pathogens under consideration.

6) Risk estimation

A risk estimation integrates the results from the release assessment, exposure assessment and consequence assessment to produce overall estimates of risks associated with the hazards. Thus, risk estimation takes into account the whole of the risk pathway from hazard identification to the unwanted consequences.

The following factors should be considered in the risk estimation:

- number of people falling ill and the proportion of that number affected with resistant strains of bacteria
- increased severity or duration of infectious disease
- number of person/days of illness per year
- deaths (total per year; probability per year or lifetime for a random member of the population or a member of a specific more exposed sub-population)
- importance of the pathology caused by the target bacteria
- absence of alternate antimicrobial therapy
- incidence of resistance observed in humans
- ~~some arbitrary scale of~~ consequences to allow weighted summation of different risk impacts (e.g. illness and hospitalisation).

7) Risk management options and risk communication

Risk management options and risk communication have to be continuously monitored and reviewed in order to ensure that the objectives are being achieved.

Appendix XXI (contd)

Article 3.9.4.3.

Analysis of risks to animal health

1) Definition of the risk

The infection of animals with bacteria that have acquired resistance from the use of a specific antimicrobial(s) in animals, and resulting in the loss of benefit of antimicrobial therapy used to manage the animal infection.

2) Hazard identification

- Bacteria that have acquired resistance, (including multiple resistance) arising from the use of an antimicrobial(s) in animals.
- Bacteria having obtained a resistance determinant(s) from ~~another~~ other bacteria which have acquired resistance arising from the use of an antimicrobial(s) in animals.

The identification of the hazard must include considerations of the class or subclass of the antimicrobial(s). This definition should be read in conjunction with point 4) of Article 3.9.4.1.

3) Release assessment

The following factors should be considered in the release assessment:

- animal species treated
- number of animals treated, sex, age and their geographical distribution
- amounts used and duration of treatment
- variation in methods and routes of administration of the antimicrobial(s)
- the pharmacodynamics/ pharmacokinetics of the antimicrobial(s)
- site and type of infection
- development of resistant bacteria
- mechanisms and pathways of resistance transfer
- cross-resistance and/or co-resistance
- surveillance of animals, ~~animal~~ products of animal origin and animal waste products for the existence of resistant bacteria.

4) Exposure assessment

The following factors should be considered in the exposure assessment:

- prevalence and trends of resistant bacteria in clinically ill and clinically unaffected animals
- prevalence of resistant bacteria in feed /the animal environment

- animal-to-animal transmission of the resistant bacteria
- number/percentage of animals treated
- dissemination of resistant bacteria from animals (animal husbandry methods, movement of animals)
- quantity of antimicrobial(s) used in animals
- treatment regimens (dose, route of administration, duration)
- survival capacity of resistant bacteria
- exposure of wild life to resistant bacteria
- disposal practices for waste products and the opportunity for animal exposure to resistant bacteria or resistance determinants in those products
- capacity of resistant bacteria to become established in animal intestinal flora
- exposure to resistance determinants from other sources
- dose, route of administration and duration of treatment
- pharmacokinetics (metabolism, bioavailability, access to intestinal flora)
- cycling of resistant bacteria between humans, animals and the environment.

5) Consequence assessment

The following factors should be considered in the consequence assessment:

- dose–response relationships
- variation in disease susceptibility of exposed populations and subgroups of ~~the~~ those populations
- variation and frequency of animal health effects resulting from loss of efficacy of antimicrobials
- changes in ~~veterinary medicine~~ practices resulting from reduced confidence in antimicrobials
- associated cost
- perceived future usefulness of the drug (time reference).

6) Risk estimation

The following factors should be considered in the risk estimation:

- number of therapeutic failures due to resistant bacteria
- animal welfare

Appendix XXI (contd)

- economic cost
- deaths (total per year; probability per year or lifetime for a random member of the population or a member of a specific more exposed sub-population)
- incidence of resistance observed in animals.

7) Risk management options and risk communication

Risk management options and risk communication have to be continuously monitored and reviewed in order to ensure that the objectives are being achieved.

The relevant recommendations (Articles 1.3.2.7., 1.3.2.5. and 1.3.2.6.) in the *Terrestrial Code* apply.

A range of risk management options is available to minimize the emergence and spread of antimicrobial resistance and these include both regulatory and non-regulatory risk management options, such as the development of codes of practice concerning the use of antimicrobials in animal husbandry. Risk management decisions need to consider fully the implications of these different options for human health and animal health and welfare and also take into account economic considerations and any associated environmental issues. Effective control of certain bacterial diseases of animals will have the dual benefit of reducing the risks linked to antimicrobial resistance, in cases where the bacterial disease under consideration has also developed antimicrobial resistance. Appropriate communication with all stakeholders is essential throughout the risk assessment process.